88 Determination of patient screen failure and dropout rates for industry-sponsored CF inhaled antibiotic studies

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Objectives: A CRO's remit is to review sponsor's protocols and assumptions as part of the RFPprocess. A key element influencing study success is to determine if realistic screen failure (SFR) and dropout rates (DOR) have been used. If either is unrealistic it can result in an under-powered study (subsequently leading to erroneous conclusions), budget overruns and/or timeline extensions.
Methods: Quintiles' proprietary databases, journal articles and the FDA's Summary Basis of Approval documents were reviewed to determine SFR and DOR for industry-sponsored CF inhaled antibiotic studies. For three pivotal placebo-controlled studies, sites randomized a mean of 15.4 patients/site (range: 13.3–29.6). Two of the three pivotal studies had a similar SFR (41.9 and 39.1%); the other study experienced a much lower SFR (6.4%). This study enrolled many young patients and was conducted in different geographical regions than the other two studies and it is unclear of how this may have influenced this metric. DOR at the end of the treatment period were very similar and ranged from 15.7 to 18.8%. It is not surprising that the two studies with a post-treatment follow up period experienced an overall high DOR (39.9 and 24.4%). The SFR and DOR for both open label studies were similar despite the difference in study length.
Conclusions: It is imperative to review data in order to adequately project key metrics such as SFR and DOR. These can be affected by entry criteria, study design and duration. It is important to select a study similar to the protocol under review to avoid common pitfalls such as underestimating the amount of patients likely to complete the entire study.

89 Evaluation of a twice daily tobramycin regimen in adult cystic fibrosis patients

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Objectives: The aims of this study were:
1. Improve the proportion of patients achieving target serum concentrations of intravenous tobramycin therapy on first dose selection.
2. Reduction in number of dose adjustments and invasive blood tests.
3. Ensure comparable efficacy and safety.

Methods: Two Tobramycin regimens were compared:
- "Standard" regimen: 10 mg/kg/day split three times daily given by IV bolus injection, serum concentrations (pre-dose and 1 hour post dose) were sampled after the third dose.
- Twice daily regimen: 120 mg/m^2 12 hourly, based on body surface area (BSA) given by IV bolus injection, serum concentrations were determined on the second dose.

In both cases doses were adjusted to achieve target concentrations of pre-dose <2 mg/L and one hour post-dose 8–12 mg/L. Serum concentrations were rechecked after 7 days or after any dose adjustment (n = 31).
Tobramycin was prescribed for Pseudomonal infective exacerbations determined on clinical assessment, with other a beta-lactam, according to local CF antibiotic guidelines for at least 2 weeks.
Primary outcome measure was proportion of patients' achieving target concentrations. Secondary outcomes were creatinine clearance, change in FEV_1, number of dose adjustments and numbers of blood tests.
Conclusion: There was a significant improvement in the proportion of patients achieving target concentration on the new regimen ($p < 0.001$). Number of blood tests and dose adjustments were significantly reduced ($p = 0.01$). Change in FEV_1 was similar for both regimens ($p = 0.8$). In conclusion, a twice daily regimen based on BSA was safe and effective for the treatment of pseudomonas exacerbations in Adult CF patients.

90 Inhalation of colistimethate dry powder (Colobreathe) results in negligible systemic exposure

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Objective: To evaluate the systemic absorption of Colobreathe, colistimethate dry powder for inhalation (CDPI) in CF subjects with chronic pulmonary infection with *P. aeruginosa* (PA).
Methods: After 72 hr washout, 34 subjects aged 6–60 yrs received 1.6625 IU CDPI twice daily for 7 days. Blood, urine and sputum were assayed using LC-MS/MS methodology.
Results: Maximum plasma concentration (Cmax) for total CMS was achieved between 0.5 and 1 hr post dose. Mean peak plasma Cmax for total CMS after the final dose was 256.8 (±106.0), 321.2 (±179.8) and 455.9 (±314.4) ng/ml for age groups 6–12 yrs, 13–17 yrs, 18+ yrs respectively. Corresponding levels for free colistin were 36.2 (±19.7) ng/ml, 35.6 (±21.5) ng/ml and 52.4 (±39.9) ng/ml. The mean sputum CMS concentrations after 7 days therapy were respectively 119.1 (±88.1) 272.1 (±226.1) and 126.8 (±88.5) mg/l. Urinary excretion of CMS was <3% of the administered dose. The AUC_{0-6} and the dose adjusted AUC_{0-6} (AUC_{0-6}/D) for total CMS were similar between children and adolescents, while higher AUC_{0-6} was observed in the adult group. When AUC_{0-6} was adjusted by dose and body weight, a slightly higher $AUC_{0-6}/D/W$ for total CMS was observed in children. High PK variability was observed in all age groups. Comparison of results versus an established legacy microbiological assay showed that this method lacked precision and sensitivity.
Conclusion: Inhalation of CDPI results in very low levels of systemic drug. This suggests limited potential for drug-drug interaction. Sputum levels are well in excess of the systemic breakpoint of PA. The predominant species is CMS and may significantly contribute to the therapeutic effect rather than colistin.

91 Sequential inhalative tobramycin–colistin-combination stabilizes patients with chronic *Pseudomonas aeruginosa* colonization

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Pseudomonas aeruginosa in the airways of CF-patients restricts the efficacy of antibiotics leading to chronic infections which have a large impact on morbidity and mortality. Antibiotic combination therapy might be more efficient than single antibiotics to combat lung infections in CF.
Methods: In an observational study 40 CF patients, suffering from chronic *P. aeruginosa* lung infection, pretreated either with Tobramycin or Colistin, were inhalatively treated three times (28 days each) with 300 mg Tobramycin (Bramitob®) twice daily followed by Colistin (1 Mio I.U.) twice daily. Lung function expressed as expiratory volume in 1 sec (FEV_1), bacterial resistance, QoL and clinical outcome were determined before, after 2 cycles and after the study.
Results: Interim analysis in 22 of 40 patients (mean age 22.9±10.2 years) showed that drugs were well tolerated by almost all patients (80%). FEV_1 increased (+3.4±13.7% absolute, +8.6±23% relative to baseline; $p = 0.14$. Without exacerbative patients +2.9±5.6% absolute and +6.4±11% relative to baseline; $p = 0.028$), coughing and sputum was reduced in >50% of patients and therapeutic outcome increased in 82% of patients detected by clinical assessment of physicians. Exacerbations rates were reduced by 44% ($p = 0.13$) and iv-treatments were also reduced by 40% ($p = 0.008$). Resistances against antibiotics increased from 11% to 21%.
Conclusion: The efficacy of tobramycin and colistin sequentially combined, suggest that combination therapy is more efficient than single antibiotic therapy to combat lung infection of *P. aeruginosa* in CF patients. Alternative combinations of inhalative antibiotics should be investigated in further trials.